Remarks

Claims 1-10 and 12-42 are pending in the present application. Claims 29 and 42 have been cancelled without prejudice. The following rejections are at issue and are set forth by number in the order in which they are addressed:

1. Claims 21, 29 and 42 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite;
2. Claims 1-10, 12-18, and 20-41 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly being nonenabled;
3. Claim 41 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly containing new matter;
4. Claim 42 stands rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Primus (Cancer Res. 53:3355-61 (1993));
5. Claim 42 stands rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Dranoff (U.S. Pat. No. 5,637,483);
6. Claim 41 stands rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Mathor (Proc. Natl. Acad. Sci. USA 93:10371-76 (1996));
7. Claims 1-10, 12-14, 16-18, 21 and 41 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Arai (Virology 260:109-115 (1999)), as evidenced by Falqui (J. Mol. Med. 77:250-253 (1999));
8. Claims 1-10, 12-14, 16-18, 20-22, 29 and 41 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Falqui (J. Mol. Med. 77:250-253 (1999) in view of Arai (Virology 260:109-115 (1999);
9. Claims 1 and 12-18 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Falqui (J. Mol. Med. 77:250-253 (1999) in view of Arai (Virology 260:109-115 (1999), and further in view of CLONTECHniques, 4/1999;
10. Claims 1, 12-14, 16, 17 and 25 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Falqui (J. Mol. Med. 77:250-253 (1999) in view of Arai (Virology 260:109-115 (1999), and further in view of Naldini (Science 272:263-267 (1996);

11. Claims 1, 22-24, 27-34, 39, 40, and 42 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Falqui (J. Mol. Med. 77:250-253 (1999) in view of Arai (Virology 260:109-115 (1999), and further in view of Primus and Deng (Biotechniques 25:274-279 (1998);
12. Claims 1, 26, and 35-38 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Falqui (J. Mol. Med. 77:250-253 (1999) in view of Arai (Virology 260:109-115 (1999), and further in view of Schroder (Bitech. Bioeng. 53:547-59 (1997));
13. Claim 41 is rejected on the ground of nonstatutory obviousness-type double patenting over U.S. Pat. No. 6,852,510.

Claims 1, 21, and 41 have been amended and Claims 29 and 42 have been canceled in order to further Applicant's business interests and the prosecution of the present application in a manner consistent with the PTO's Patent Business Goals (PBG; 65 Fed. Reg. 54603 (September 8, 2000), and not in acquiescence to the Examiner's arguments and while reserving the right to prosecute the original (or similar) claims in the future. None of the claim amendments made herein are intended to narrow the scope of any of the amended claims within the meaning of *Festo Corp. v. Shokestu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558, 56 USPQ2d 1865 (Fed. Cir. 2000) or related cases.

1. The Claims are Definite

Claims 21, 29 and 42 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Claims 29 and 42 have been cancelled, thus the rejection with respect to those claims is moot. Claim 21 has been amended to refer to "secretion" signal sequences. Accordingly, each of the Examiner's grounds for rejection have been addressed and Applicants respectfully request removal of this rejections.

2. The Claims are Enabled

Claims 1-10, 12-18, and 20-41 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly being nonenabled. Applicants respectfully disagree.

The rejection is traversed because the Examiner has failed to establish a *prima facie* case

of non-enablement. The standard to be applied in assessing enablement is whether the experimentation needed to practice the claimed invention is undue or unreasonable. *See* TRAINING MATERIALS FOR EXAMINING PATENT APPLICATIONS WITH RESPECT TO 35 U.S.C. SECTION 112, FIRST PARAGRAPH-ENABLEMENT CHEMICAL/BIOTECHNICAL APPLICATIONS, *citing In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). When applying this standard, the burden is on the Examiner to make a *prima facie* case of non-enablement that is well grounded in scientific reasoning or evidence. *See In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993); *See also* MPEP §706.03 and §2164.04. This is because without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling (*Wright,* 27 USPQ2d at 1513).

The specification provides extensive examples demonstrating methods for transducing host cells. See, e.g., examples 2-19, 26-28. The specification also describes in detail how to use these methods to serially transduce cells. See, e.g., Specification at 47:4-48:10. The Specification also provides that the a host cell produced by this method can have from 10 to more than 100 copies of a retrovirus integrated into its genome. ("In some embodiments, the genome comprises at least 5, and preferably, at least 100 integrated integrating vectors." Specification 3:25-26). Applicants agree that the prior art cited by the Examiner (i.e., Arai and Coffin) teach away from methods involving serial transduction at a high multiplicity of infection. This is precisely why the presently claimed invention is not obvious in view of the prior art. However, as indicated in the specification, the present inventors have found that the claimed process is useful for engineering cells to produce proteins for purification. This is in part due to the fact that the methods taught in the specification utilize large starting populations of cells and selection procedures to select cells that produce high levels of protein and that also have high numbers of integrated retroviral vectors in their genomes. Based on the teaching of the specification, obtaining the claimed number of integration is within the skill in the art whether or not the prior art teaches away from such procedures. What the present Specification enables and what the prior art teaches away from are two separate issues. As such, the claims are enabled. Applicants respectfully request that this ground of rejection be removed.

3. The Claims do not Contain New Matter

Claim 41 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly containing

new matter. Claim 1 has been amended to include a similar limitation. In particular, the Examiner states in Para. 15 that:

> Page 4, lines 7-8 states that at least 2, 5, and 10 vectors will integrate. Page 5, line 4 states that at least 5 and at least 10 integrated copies would be present. Page 44, lines 25 and 26 states that 'host cells contain from 2 to 100 copies of the integrated vectors, and preferably from 5 to 50 copies of the integrated vector." Then Examples 19, 22, 25, and 26 provide exemplification of numbers of integrants achieved. These are not expressed as number of integrants per cell, and as such no mention of 20 integrants is given. Further, as argued above, the maximal number of integrants apparent is about 13. Therefore, as the specification does not provide support for these new limitations, the limitations constitute impermissible new matter."

The Examiner's attentions is respectfully directed to the Specification, page 3:25-26: "In some embodiments, the genome comprises at least 5, and preferably, at least 100 integrated integrating vectors." The specification clearly teaches a range integrated vectors in a single cell of 5 to at least 100. Thus, the Examiners argument that "these are not expressed as number of integrants per cell" is incorrect. Furthermore, Applicants assert that the passages cited by the Examiner do indeed describe numbers of integrants per cell. The Examiner is apparently arguing that the entire population contains only 100 integrants, e.g., 100 integration events spread across the entire population of cells. This interpretation is clearly wrong when the specification is considered as a whole. The goal of the methods described in the specification is clearly to create clonally selected cell lines in which each cell (the cells in the clonally selected line are identical) contains a high number of integrated vectors. This is directly opposite of the situation where the entire population would only comprise 100 integrated vectors.

As can be seen, the claimed range of 20 to 100 integrated vectors is clearly within the described range of 5 to 100 integrated vectors per cells. As such, the claim limitation of 20 to 100 integrated vectors per cell is supported by the specification. Applicants respectfully request that this ground of rejection be withdrawn.

4, 5, 6, 7. The Claims are Novel Over the Cited References

Claim 42 stands rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Primus (Cancer Res. 53:3355-61 (1993)); Claim 42 stands rejected under 35 U.S.C. §102(b) as

allegedly being anticipated by Dranoff (U.S. Pat. No. 5,637,483); Claim 41 stands rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Mathor (Proc. Natl. Acad. Sci. USA 93:10371-76 (1996)); Claims 1-10, 12-14, 16-18, 21 and 41 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Arai (Virology 260:109-115 (1999)), as evidenced by Falqui (J. Mol. Med. 77:250-253 (1999)).

Claim 42 has been cancelled. Thus the rejections of the claim are moot. Claims 1 and 41 from 20 to 100 retroviral integrations in a host cell. As admitted by the Examiner in para. 12 of the Office Action, the art of record does not teach how to achieve greater than 15 integrations. As such, the claims are not anticipated by the cited references. Applicants respectfully request that these grounds of rejection be removed.

8, 9, 10, 11, 12. The Claims are Not Obvious

Claims 1-10, 12-14, 16-18, 20-22, 29 and 41 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Falqui (J. Mol. Med. 77:250-253 (1999) in view of Arai (Virology 260:109-115 (1999); Claims 1 and 12-18 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Falqui (J. Mol. Med. 77:250-253 (1999) in view of Arai (Virology 260:109-115 (1999), and further in view of CLONTECHniques, 4/1999; Claims 1, 12-14, 16, 17 and 25 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Falqui (J. Mol. Med. 77:250-253 (1999) in view of Arai (Virology 260:109-115 (1999), and further in view of Naldini (Science 272:263-267 (1996); Claims 1, 22-24, 27-34, 39, 40, and 42 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Falqui (J. Mol. Med. 77:250-253 (1999) in view of Arai (Virology 260:109-115 (1999), and further in view of Primus and Deng (Biotechniques 25:274-279 (1998); Claims 1, 26, and 35-38 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Falqui (J. Mol. Med. 77:250-253 (1999) in view of Arai (Virology 260:109-115 (1999), and further in view of Schroder (Bitech. Bioeng. 53:547-59 (1997)). For the Examiner's convenience, these rejections are considered together because the same traversal is relevant to each rejection.

A *prima facie* case of obviousness requires the Examiner to provide a reference(s) which (a) discloses all of the elements of the claimed invention, (b) suggests or motivates one skilled in the art to combine the claimed elements to produce the claimed combination, and (c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of these three requirements precludes a finding of a *prima facie* case of

obviousness and without more entitles the Applicants to allowance of the claims in issue. *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990).

The cited references in combination do not teach each element of the claims.[1] As amended, the claims require 20 to 100 integrated retroviral vectors per host cell. As admitted by the Examiner in para. 12 of the Office Action, the art of record does not teach how to achieve greater than 15 integrations. Moreover, the Examiner has drawn unsupported conclusions from Falqui and Arai and thus those references are not properly combined in any of the rejections. In particular, the Examiner argues in para. 10 that "It is clearly apparent from from the data presented in Figures 1 and 2 that this serial transduction protocol leads to multiple integrations of the retrovirus in each cell (see above)." This simply is not true. The data in Falqui establishes that more cells are transduced, not that the individual cells contain multiple integrations. There is no attempt in Falqui to clonally isolate cells and determine the copy number of integrated vectors. Moreover, the fact that some of the cells express higher levels of GFP can be explained by either 1) the fact that the accumulation of GFP within the cells over the longer serial transduction period (i.e., cells transduced in the first round have a longer time to express and accumulate GFP) or 2) by the fact that when more cells are transduced, the higher the chance that some cells with a single integration event will simply produce more GFP and other cells with a single integration event. Thus, Falqui does not support the proposition for which the Examiner has cited it.

Neither Falqui nor Arai, alone or in combination, teach or suggest 20 to 100 integrated retroviral vectors per host cell. Additionally, as admitted by the Examiner in para. 39, Falqui and Arai do not teach clonal selection and purification of a protein of interest. Thus, a prima facie case of obviousness is not established for Claims 1-10, 12-14, 16-18, 20-22, 29 and 41, which stand rejected under 35 U.S.C. §103 as allegedly being obvious over Falqui (J. Mol. Med. 77:250-253 (1999) in view of Arai (Virology 260:109-115 (1999). As such, this ground of rejection should be removed.

Neither Falqui, Arai, nor CLONTECHniques, alone or in combination, teach or suggest

[1] Because the failure to teach each element of the claims is dispositive, Applicants have not addressed the Examiner's arguments regarding motivation to combine and reasonable expectation of success. Applicants do not waive the these arguments and do not believe the references are properly combinable or that the references, alone or in combination, provide a reasonable expectation of success in arriving at the claimed invention. Applicnats expressly reserve the right to advance these arguments in the future.

20 to 100 integrated retroviral vectors per host cell. Additionally, as admitted by the Examiner in para. 39, Falqui and Arai do not teach clonal selection and purification of a protein of interest. CLONTECHniques does not remedy this deficiency. Thus, a prima facie case of obviousness is not established for Claims 1 and 12-18, which stand rejected under 35 U.S.C. §103 as allegedly being obvious over Falqui (J. Mol. Med. 77:250-253 (1999) in view of Arai (Virology 260:109-115 (1999), and further in view of CLONTECHniques, 4/1999. As such, this ground of rejection should be removed.

Neither Falqui, Arai, nor Naldini, alone or in combination, teach or suggest 20 to 100 integrated retroviral vectors per host cell. Additionally, as admitted by the Examiner in para. 39, Falqui and Arai do not teach clonal selection and purification of a protein of interest. Naldini does not remedy this deficiency. Thus, a prima facie case of obviousness is not established for Claims 1, 12-14, 16, 17 and 25, which stand rejected under 35 U.S.C. §103 as allegedly being obvious over Falqui (J. Mol. Med. 77:250-253 (1999) in view of Arai (Virology 260:109-115 (1999), and further in view of Naldini (Science 272:263-267 (1996). As such, this ground of rejection should be removed.

Neither Falqui, Arai, Primus, or Deng, alone or in combination, teach or suggest 20 to 100 integrated retroviral vectors per host cell. Thus, a prima facie case of obviousness is not established for Claims 1, 22-24, 27-34, 39, 40, and 42, which stand rejected under 35 U.S.C. §103 as allegedly being obvious over Falqui (J. Mol. Med. 77:250-253 (1999) in view of Arai (Virology 260:109-115 (1999), and further in view of Primus and Deng (Biotechniques 25:274-279 (1998). As such, this ground of rejection should be removed.

To the extent that the Examiner contends that it would be obvious to modify these references to provide the element of 20 to 100 integrated retroviral vectors per host cell, Applicants contend that such a modification is improper. Two references cited by the Examiner, Coffin and Arai, establish that the prior art teaches away from introducing from 20 to 100 retroviral vectors into the genome of a host cell. As taught in Coffin: "Insertional mutagenesis by retroviral vectors is often cited as a safety concern . . . . In situations where relatively few cells are modified, as in the case of gene transfer into rare hematopoietic stem cells, the total number of insertion sites will also be small, and the risks are expected to be very low. The risks are higher in cases where large numbers of cells are transduced, which increases the number of independent integration events. . . ." As taught by Arai (Virology 260:109-115 (1999)): high

levels of proviral integration could result in "insertional mutations in essential genes."

Applicants respectfully remind the Examiner that where references teach away from the claimed invention, there can be no motivation to modify the references. *See Tec Air, Inc. v. Denso Manufacturing Michigan, Inc.*, 192 F.3d 1353 (Fed. Cir. 1999). In this instance, there is no motivation to modify the references to provide host cells comprising 20 to 100 integrated vectors per cell because a person of skill in the art would fear insertional mutagenesis. Applicants note that this reasoning is not inconsistent with the reasoning offered regarding enablement because it is the present application which enables producing host cells with high numbers of integrated retroviral vectors. The prior art teaches away from such methods.

Neither Falqui, Arai, nor Schroder, alone or in combination, teach 20 to 100 integrated retroviral vectors per host cell. Additionally, as admitted by the Examiner in para. 39, Falqui and Arai do not teach clonal selection and purification of a protein of interest. Schroder does not remedy this deficiency. Thus, a prima facie case of obviousness is not established for Claims 1, 26, and 35-38, which stand rejected under 35 U.S.C. §103 as allegedly being obvious over Falqui (J. Mol. Med. 77:250-253 (1999) in view of Arai (Virology 260:109-115 (1999), and further in view of Schroder (Bitech. Bioeng. 53:547-59 (1997)). As such, a prima facie case of obviousness has not been established and applicants respectfully request that this ground of rejection be removed.

13. Double patenting

Claim 41 is rejected on the ground of nonstatutory obviousness-type double patenting over U.S. Pat. No. 6,852,510. Upon resolution of the remaining rejections, Applicants will submit a terminal disclaimer to overcome this rejection.

CONCLUSION

All grounds of rejection and objection of the Office Action of November 17, 2005 having been addressed, reconsideration of the application is respectfully requested. It is respectfully submitted that the invention as claimed fully meets all requirements and that the claims are worthy of allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: February 17, 2006

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